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OPINION

Hiding in plain sight: an evolutionary approach to the South American Zika outbreak and its future consequences

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ABSTRACT. Emerging Infectious Diseases (EID) pose a world-wide health and socio-economic threat. Accelerating climate change and globalization are exposing unforeseen ways that pathogens cope with their surroundings. The 2015 Zika virus (ZIKV) outbreak was an example of expansion into previously inaccessible fitness spaces, causing a sudden epidemic. Recent studies indicating the subsequent decrease in symptomatic cases means the virus is in remission, currently poses little threat, and therefore can be ignored. We present an evolutionary scenario derived from the Stockholm Paradigm, of oscillating phases of expansion and isolation, accompanied by changes in transmission, persistence, virulence, and pathology. Chief among these is the likelihood that asymptomatic strains are constantly transmitted sexually. This suggests that the currently quiescent virus retains capacities to reemerge abruptly and spread rapidly in an arena of changing opportunity.

KEY WORDS. Emerging Infectious Disease, outbreaks, Stockholm Paradigm, Zika virus.

Background

Emerging Infectious Diseases (EID) constitute a global threat to humans and the animals and plants upon which they depend socio-economically. And while there appears to be a general evolutionary dynamic relating emerging diseases with climate change (Brooks and Boeger 2019, Brooks et al. 2019, Hoberg and Brooks 2015), each new emergence event reveals novel dimensions about pathogen capabilities. One of the most notable is a new variant of the Asian strain of Zika virus (ZIKV), source of the highly publicized New World outbreaks of 2015.

The rapidity with which Zika emerged in Latin America, coupled with a high proportion of neurological deficits in babies born to Zika-positive mothers warranted special attention. How did it come to be in the New World and why did it behave differently there? These issues were discussed peripherally, but initial reaction was muted. Reports identified seasonal changes in mosquito dynamics or herd immunity as the underlying cause of the pandemic (Silva et al. 2017). Vaccine-development and vector-control plans were hastily initiated, but before any of them bore fruit, the disease seemingly disappeared, undermining calls for further action (Cohen 2018). It is highly unlikely that a virus with a half century history of epidemics can simply vanish after the most recent and severe outbreak. Additionally, the Asian strain, against which complete immunity was reported in monkeys (Dudley et al. 2016) has already caused three additional outbreaks in Asia and South-America. In this opinion piece, we draw attention to aspects of the evolutionary biology of Zika that may help explain how a previously insignificant disease became a major threat to infant neural development, why it could recur, and why it could become a global problem.

Transmission

Most studies describe Zika as a 'mosquito-borne arbovirus' (Dick 1952, Duffy et al. 2009, Mladinich et al. 2017, Smith et al. 2018). The virus was first collected from rhesus monkeys, and subsequent studies showed that the mosquitoes *Aedes africanus* (Theobald, 1901) and *Aedes aegypti* (Linnaeus, 1762) were competent vectors of the pathogen (Dick 1952).

Within twenty years of its discovery, a variant of Zika was found in southern Asia, and was detected in local mosquito populations. The Asian strain was little studied until a 2007 outbreak on the island of Yap was suspected of infecting thousands of people (Duffy et al. 2009). In 2015, the largest outbreak yet resulted in thousands of cases of microcephaly in Brazil and emergences of

Guillain-Barré syndrome in the South-Pacific and in Colombia (Mendez et al. 2017). As expected, medical and epidemiological research scrambled to get a hold of the new virus, and studies initially focused on controlling the suspected vector *A. aegypti*. It is not completely without base to assume that the mosquito transfers Zika, since closely related viruses (chikungunya and dengue) have stable populations in South-America and are transmitted by *A. aegypti*. Nevertheless, although this mosquito is still a competent vector of the African strain, it transmits the American and Asian Zika strains much less efficiently (Roundy et al. 2017). Additionally, none of the widespread, related mosquito species seem capable of transmitting the virus (Dodson et al. 2018). Furthermore, the peak of Zika related cases appears to have been sustained outside of the mosquito-breeding season, which suggests the existence of an alternate transmission route underlying a vector-borne pathway (Ferdousi et al. 2019).

We must revisit previous cases and explore a neglected aspect of Zika biology. Along with the sudden change in virulence, the 2007 Zika outbreak in Yap produced one of the first documented cases of the sexual transmission of the virus (Foy et al. 2011, Sakkas et al. 2018). Little studied at the time, the number of documented cases of sexually acquired Zika has increased (Moreira et al. 2017). Furthermore, human male patients shed Zika RNA in the semen six months after the remission of their clinical symptoms (Barzon et al. 2016), and the virus increases the rate of spermiogenesis (Sakkas et al. 2018). With as many as 80% of infected adults reporting no symptoms, sexual contact could be an effective mode of transmission (Freour et al. 2016).

Phylogenetic studies show that Zika originated in Africa and dispersed to Asia, likely as a result of human migrations approximately 60 years ago (Smith et al. 2018). There is evidence that a sexually transmitted strain or genotype of Zika was present in the African lineage (Sakkas et al. 2018), along with the common vector-borne strain. When expanding its distribution to Asia, Zika faced new mosquito taxa, but the human host remained constant. The sexually-transmitted variant (Sakkas et al. 2018) had the advantage of not having to expand to new vectors and its prevalence seems to have been amplified by selection as a result. The Asian strain introduced to the New World thus already had an enhanced capacity for sexual transmission relative to the African strain. Zika must be seen as a virus that persists through an interconnected network of both vectored and sexual transmission, increasing and expanding the risk factors associated with potential pandemics (Ferdousi et al. 2019).

Pathogenicity and virulence

Pathogen-host associations do not always produce disease, even when the pathogen multiplies extensively in the host. As well, though in many pathogens (e.g. Influenza A and B virus) a high pathogen replication rate is associated with elevated pathogenicity (the potential of the pathogen to cause disease in a single host specimen), virulence (the measure of how much damage a pathogen causes to the host) is not necessarily associated with high rates of infection (e.g. Hepatitis C virus), whereas an asymptomatic disease may spread through a high number of propagules (e.g. Herpes simplex virus) (Anderson and May 1982, May and Anderson 1983).

Experiments using mouse models show that diverse Zika lineages exhibit striking differences in both pathogenicity and virulence. African strains were 10,000-fold more virulent, and produced uniformly fatal disease in mouse models, as opposed to the significantly lower mortality rate of the Asian strain (Smith et al. 2018). When comparing various Asian strains with the one related directly to that responsible for the American outbreak, the Asian strain showed 10 to 100-fold higher titer numbers and a nine times higher mortality than the American (Beaver et al. 2018). If vector-borne transmission was overshadowed by sexual transmission in the evolution of Zika in Asia, efficient infection would rely increasingly on host condition (Ewald 2004) explaining the apparent decrease in both virulence and pathogenicity. Studies of these two measures on human populations revealed that asymptomatic infections were substantially lower during African outbreaks than during Asian ones (Simonin et al. 2017); 80% of the Yap Island cases are thought to have been asymptomatic (Duffy et al. 2009).

These data suggest that the Asian strain of Zika introduced to the New World had made the evolutionary transition from primarily vector-transmitted to primarily sexually-transmitted. With the majority of the cases being asymptomatic, the extent to which the STD variant has spread through human populations is hard to estimate. Nevertheless, the distance the virus has traveled and the speed with which it conquered the Americas suggests a novel STD variant underlying the visible outbreaks. Additionally, given the high rate of asymptomatic cases, it is by now extremely difficult to tie the presence of ZIKV to registered outbreaks, since most carriers in between outbreaks and during the 2015 Brazilian outbreak most likely never produced symptoms. We must therefore assume that the distribution of the virus shows a significant mismatch with that of documented outbreaks. That contention is consistent with general observations of pathogen distribution, where the geographic range of the pathogen is always larger than the distribution of disease (Audy 1958).

Pathology

The pathology of the South American strain set this epidemic apart from previous outbreaks. Microcephaly, Guillain-Barré syndrome and neural damage had never before been associated with the ZIKV, and were the main reasons the American Zika qualified as an EID (Petersen et al. 2016). The question of 'how did the virus acquire new pathological characteristics' immediately surfaced. Genetic screening found a VNDT sequence motif in the virus strand capable of neuro-invasion (Annamalai et al. 2017), which was able to cross the blood-brain-barrier through infecting microvascular endothelial cells (Mladinich et al. 2017). Using the same patho-mechanism, this strain can also pass through the placenta, enter the brain of the embryo

and cause serious neural damage (Ahmad et al. 2018, Mladinich et al. 2017). This VNDT motif is polymorphic in both African and Asian strands, but American ZIKV isolates carry only the one VNDT morph (Mladinich et al. 2017), suggesting a recent change in the genome of the virus. Additionally, the abrupt loss of genetic variation in the newly emergent American strand corresponds with the founder effect (Provine 2004), when a small subset of the original population establishes a lineage, with different characteristics due to the decreased genetic variation. When applied to Zika, the Brazilian lineage is derived from the VNDT morph capable of neuro-invasion and represents a subset of the original ZIKV populations. Furthermore, recent studies showed that ZIKV is capable of causing long-term fetal developmental anomalies, including autism spectrum disorder, and other than neural damage, and poses a threat to pregnant mothers, regardless of the declining epidemic (Chakhtoura et al. 2018, Vianna et al. 2018, Walker et al. 2019).

A Specific Case of a General Principle

The Zika story highlights all the elements of the Stockholm Paradigm (Textbox 1). Beginning in Africa, where it is primarily a mosquito-transmitted pathogen, in keeping with the ancestral legacy of its closest relatives. African ZIKV also demonstrates plasticity in transmission, being capable of sexual transmission at a low level. When climate changes created hospitable connections out of Africa through the Arabian peninsula, ancestral ZIKV expanded geographically into Asia via ecological fitting. During this *generalization in geographical fitness space*, ZIKV was exposed to novel mosquitos but the same ancestral vertebrate hosts (including humans). That *generalization in host fitness space* led to decreased and diffuse selection focused on mosquito transmission with concomitant increased and focused selection on sexual transmission, produced an isolated, specialized form of ZIKV in Asia. The new specialized Asian form became what it is today, predominantly a sexually transmitted pathogen that

Textbox 1. The Stockholm Paradigm.

For more than 60 years, pathogens and hosts have been envisioned as engaged in evolutionary arms races, each participant mutually modifying the other. The increasing specialization of a pathogen with respect to a given host should be accompanied by decreasing ability to survive in association with other hosts. In order to switch to a new host, therefore, a pathogen must first evolve novel host-use capacities and then colonize a suitable new host. Given the absence of a mechanism by which such mutations could emerge in response to the presence of any particular novel host, coevolution has been viewed as a kind of firewall against emerging disease; host switches should not be common (Thompson 1994, Wolfe et al. 2007). And yet, host switching happens often in real time and phylogenetic studies indicate that host switching has always been common (Brooks and Boeger 2019, Hoberg and Brooks 2008, 2015). This has been called the *Parasite Paradox*; how can ecologically specialized pathogens switch hosts easily?

The Stockholm Paradigm resolves the paradox by recognizing the influence of two fundamental but often overlooked aspects of Darwinian evolution. First, *inherited traits of adaptive significance may be highly specialized but are also phylogenetically conservative* (Brooks and McLennan 2002, Darwin 1872). The conservative nature of pre-existing specialized adaptations, aided by phenotypic plasticity and co-option produces *ecological fitting* (Agosta et al. 2010, Brooks and McLennan 2002, Janzen 1985), the ability of pathogens to take advantage of novel host opportunities based on pre-existing specializations. Entire pathogen communities ranging across a geographically expansive wide range of habitats, may be structured by ecological fitting (Brooks et al. 2006), suggesting that the potential for changing hosts through ecological fitting is large (fitness space is "sloppy": Agosta 2006, Agosta and Klemens 2008). Second, strong coevolutionary arms race dynamics are intimate affairs, affecting a given pathogen and a given host at a given place. As a result, they have no impact on other potential pathogen-host associations in other places. The efficacy of a coevolutionary arms race is weakened in proportion to the number of different hosts occupied. Modelling efforts show that, as hosts are added, specialized coevolutionary arms race dynamics become generalized Red Queen dynamics in which the pathogen has all the advantages, because all hosts are focused on a single pathogen while the pathogen can take advantage of variation among multiple hosts (Araujo et al. 2015, Braga et al. 2018, Brooks et al. 2019). Environmental perturbations change the opportunity space for pathogens, altering trophic structures and geographic distributions. They increase the chances that a pathogen will encounter susceptible, but previously unexposed, hosts. Highly specialized pathogens become more generalized by virtue of occupying a larger proportion of susceptible hosts. Environmental stability reduces connectivity in fitness space, producing localized isolated pathogen-host associations in which novel specialized variants may arise and survive. Though arising in a localized context, such novel variants often have substantial potential for ecological fitting whenever the next perturbation creates new opportunities. Over long periods of time, pathogen diversity is thus shaped by increases and decreases in host range (the Oscillation Hypothesis: Janz and Nylin 2008, Janz et al. 2006) and expansions and isolations in geographic distribution (the Taxon Pulse: Erwin 1981, Halas et al. 2005). The Stockholm Paradigm thus identifies a critical, but simple role for climate change in the evolution of emerging diseases. Disease emergence occurs when pathogens are given the opportunity to explore more widely in fitness space based on pre-existing specific, yet phylogenetically conservative traits. In today's world, such opportunities are being provided not only by the current episode of climate change, but also by increasing population density and hyper-connectivity of an increasing urbanized technological humanity.

retains some capacity for facultative transmission by mosquitos. As anticipated by the Stockholm Paradigm, the isolation of ZIKV in Asia allowed novel capacities to emerge – cases of sexual transmission are documented during the 2007 outbreak (Foy et al. 2011) and transmission efficiency of the original arthropod vector decreased significantly (Roundy et al. 2017). At this point, the evolutionary trajectory for ZIKV involved oscillation from an initial single specialized form, subsequently to a generalized form and most recently expansion of two current forms. Further geographic expansion into the Pacific was accomplished by human agencies, leading to long-distance colonization by small founder populations of the Asian ZIKV, characterized by genetic changes. Asian ZIKV initially became more generalized in geographical fitness space globally, but quickly began showing evidence of founder effect divergence. For example, a founder population of one of those strains was subsequently introduced to South America. There, novel capacities in microhabitat preferences, namely, the brain and developing fetuses allowed the emergent South American ZIKV to rapidly expand into novel microhabitat fitness space. High human population densities in urban centers, coupled with transportation of people and goods led to a rapid dispersion (generalization) of the new form in geographical fitness space. Somewhat more slowly, but inexorably, novel vertebrate hosts were colonized and the virus spread geographically. It is likely that mosquito-borne transmission plays a crucial role in expanding the host range of the virus.

Anticipate to Mitigate

The most effective time to mitigate the impacts of emerging disease is during the ecological fitting phase, when pathogens are expanding their geographical distributions and host ranges according to pre-existing (and thus predictable) capacities. The DAMA protocol (Brooks et al. 2019, 2014) is based on this principle.

We know many of the capacities of the virus, which allows us to anticipate what it could be doing now and could do in the future: (1) spread geographically gradually with climate change migration, rapidly with human assistance; (2) spread among host species by mosquitos; (3) spread within hosts by sexual transmission; and (4) cause damage to fetuses and neurological problems in all infected people.

Mitigating the damage caused by Zika means mitigating transmission. This can occur (in order of increasing cost) through protected sex; through screening both partners before conception; and by massive screening of all men and women, in countries where ZIKV is known to exist (to mitigate the next outbreak) and in countries where it is not yet known to exist (to mitigate its introduction and spread). As an emergent STD, Zika is just the most recent reminder of the significance of protected sex. Regular screenings, identical to those applied for the diagnosis of Herpes, HIV, Chlamydia and many other STDs should also screen for ZIKV, and public attention should be drawn to the elevated likelihood of acquiring Zika through intimate relationships.

These efforts will not eradicate the virus. They will help us buy time, postponing and mitigating the spread and impact of the next outbreak. During that time, we need to be assessing the possible connection between Zika and infertility. Viral infections are not considered major causes of such health problems, despite a large body of evidence of their capabilities in that regard. For example, immune reaction against trophoblasts can result in miscarriage or stillbirth. In line with these predictions, sexually transmitted viruses have already been demonstrated to terminate pregnancy at an early stage (Apari et al. 2014). Szaba et al (2018) found that ZIKV causes most developmental damage by inducing cross-immunity in the early stages of pregnancy. During embryonic development, the anti-tumor Type I interferon (IFN) is impaired to protect trophoblasts exhibiting tumor-like characteristics (Budhwani et al. 2018, Soundararajan and Jagannadha Rao 2004). Exposure to Zika reactivated IFN and triggered an immune reaction against the trophoblasts. As well, recent studies showed that the suppression of the interferon response also enables ZIKV to increase fibroblast growth factor expression, thereby enhancing spread of the virus to fetal glial cells and neurons (Limonta et al. 2019). Apart from causing neural damage, the virus has the potential to cause infertility. We suggest analyzing rates of miscarriages and stillbirths in affected areas before and after the outbreak. Female ZIKV patients should be monitored for spontaneous abortions or infertility issues.

The evolutionary story of ZIKV is fascinating, and the virus has become an important emergent pathogen. Strip away the unique details of this particular virus, however, and we find that ZIKV has been engaged in evolutionary business as usual for pathogens experiencing climate change events. That any pathogen can use climate change events to the extent allowed by their pre-existing capacities is a given. That those explorations of new connections in fitness space will lead to unanticipated innovations is also a given.

The alarming rise in microcephaly cases attracted international attention, because the symptoms of early neural-damage were easily noticeable. But other aspects of the pathogen's pathology are far less conspicuous. Zika continues to exist in areas where it has been reported previously and has increased its geographic range since the 2015 outbreak in South America. With the recognition that Zika is a significant STD risk, with more than 80% of infected humans being asymptomatic, and with non-human vertebrate hosts being added to ZIKA's host range, we must use this as a teachable moment about the potential impacts of business as usual for pathogen evolution during periods of climate change perturbations (Brooks et al. 2019).

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